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HUMAN ADAPTATION TO THE TIBETAN PLATEAU

Midterm Report

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Humans live at high altitude for longer periods of time on the Tibetan Plateau than elsewhere in the world, thus providing opportunity to investigate the physiologic effects of longer (years to generations) duration of high altitude exposure. This has military importance because persons are stationed at high altitude locations for extended periods and some of the symptoms of failure to adjust to high altitude require months or years for development. Through collaborative studies involving the University of Colorado and several institutions in China we have completed two field projects (Fall 1987 and 1988) which suggest that Tibetans (natives) possess superior O_2 transport and/or utilization systems compared to acclimatized newcomers (Han "Chinese"). Studies conducted in the period covered by this report addressed the control of breathing and blood oxygenation during sleep. In 22 healthy young men (11 Tibetans, 11 Hans), measurements of the control of breathing and lung volume during wakefulness were examined together with nighttime studies of breathing and brain blood flow during sleep. Similar, additional studies were carried out in 8, principally Han patients with chronic mountain sickness and 8 age-matched, healthy controls. The data analysis from these studies is not yet complete but suggests that the Tibetans' greater lung volume, ventilatory sensitivity to hypoxia and high frequency respiratory pattern may confer protection against sleep-disorderd breathing and thus better pressure blood oxygenation during sleep. Conversely, persons developing chronic mountain sickness may be disadvantaged by a loss of ventilatory responsiveness to hypoxia with prolonged

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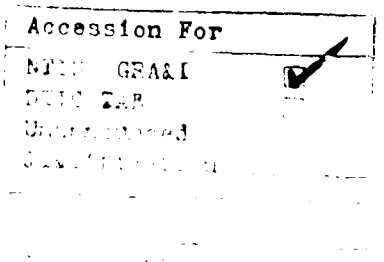
19. continued . . . altitude exposure and an inability to increase brain blood flow during periods of apnea (or hypopnea) during sleep. Population and/or individual differences in susceptibility to altitude disorders may be predicted on the basis of an individual's intrinsic lung volume, ventilatory and brain blood flow charateristics.



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FOREWORD

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HUMAN ADAPTATION TO THE TIBETAN PLATEAU

INTRODUCTION

The overall purpose of the project is to determine whether Tibetans possess special abilities to transport and utilize oxygen and whether some Hans (Chinese) lack the necessary oxygen transport characteristics to enable high altitude adaptation. While suggestions have been made that Tibetans employ a distinctive pattern of physiologic high altitude adaptation (1,2,5,6,14), comparatively little investigation has been carried out to determine the responsible mechanisms or even whether true population differences exist. The program is a collaborative effort between the University of Colorado, the Tibet Institute of Medical Sciences and the Academia Sinica Institute of Physiology (Shanghai).

Initial studies were carried out in the Fall 1987 by members of the above three groups which supported the general hypothesis that Tibetans are better adapted to high altitude than resident Chinese. More specifically, results from our Fall 1987 studies indicated that Tibetans compared to Hans residents at 3658 m had:

(1) higher maximal oxygen uptake and maximal work capacity,
(2) larger chest circumferences and forced vital capacity,
(3) increased acute hypoxic and hypercapnic ventilatory responsiveness,
(4) a respiratory pattern characterized by a high frequency and low tidal volume and
(5) heavier birth weight infants.

These observations support the possibility of superior oxygen transport and/or utilization on the part of the Tibetans compared to the Hans and suggest that Tibetans differ from other high altitude residents by virtue of having preserved hypoxic ventilatory responsiveness, unlike North and South American high altitude residents (9,11), and being able to achieve greater maximal O_2 transport than acclimatized newcomers. Interestingly, the Tibetans appear to be advantaged by a large vital capacity and possibly lung volume, in contrast to a previous report that Tibetan lung volume was not enlarged (2). However, our initial studies do not identify the source or sources of such superior abilities but suggest that advantage may be gained at each step of the oxygen transport chain; namely increased ventilatory function, greater alveolar-arterial oxygen diffusion, greater cardiac and circulatory function and increased tissue oxygen extraction.

BODY

Studies were carried out during October through November 1988 to describe characteristics of oxygen transport in healthy and unhealthy residents of high altitude during sleep. Emphasis was placed on the role of ventilation and ventilatory control parameters and on brain blood flow for determining oxygen transport during sleep. These studies enjoyed the full cooperation from the Ministry of Health in Tibet, the local Government in Tibet, the Ministry of Foreign Affairs, the Chinese Customs Authority, the People's Provencial Hospital in Lhasa, and the Tibet Institute of Medicai Sciences. Two sets of studies were carried out: the first being conducted in healthy young Tibetan and Han men and the second being performed in older Han men with chronic mountain sickness and in healthy controls.

The first study involved ventilatory and brain blood measurements in 11 healthy male Tibetans and 11 healthy male Hans to test the hypothesis that Tibetans better preserve arterial oxygen saturation during sleep. In support of the hypothesis, we had observed last year that Tibetans exhibited higher hypoxic ventilatory drives and a "fly wheel" respiratory pattern which may be expected to better sustain breathing during sleep. However, we had also observed that Tibetans had increased hypercapnic ventilatory responsiveness which could be expected to raise

the carbon dioxide threshold required to stimulate breathing during sleep and thus increase the occurrence of sleep disordered breathing.

For the assessment of ventilation and ventilatory control, forced vital capacity was measured in triplicate and helium dilution techniques were used for the measurement of functional residual capacity and the calculation of total lung volume. During room air breathing, resting ventilation and end tidal gases were monitored for at least five minutes. Oxygen uptake and CO_2 production were determined by measuring fractional CO_2 and O_2 concentration using well calibrated gas analyzers and expired volume using a Parkinson Cowan ventilation meter. Isocapnic hypoxic ventilatory responses were measured in triplicate using a modified rebreathing technique during which we induced progressive hypoxia by having the subjects rebreathe room air into a recording 13.5 spirometer. Isocapnia was maintained at the endtidal CO_2 tension measured during room air breathing by regulating the amount of expired gas shunted through a canister containing CO_2 absorber. We have shown this technique to agree well with the simultaneous measurement of hypoxic ventilatory response using the open circuit method well-established in this laboratory.

A Doppler Ultrasound Method was used to assess flow velocity in the internal carotid artery. The Doppler instrument was a prototype developed by us which is capable of operating either in pulsed or continuous mode with a variety of transducers. For the present study, the instrument was used in the pulsed mode with a four cycle transmit time and a 5 mHz transducer 6 mm in diameter. All measurements were performed with the subject seated or lying comfortably with the transducer placed near the angle of the jaw to enable insonation of the internal carotid artery. The Doppler range found to give maximum velocity signals was between 1 - 2 cm. The internal carotid was identified by its continuous diastolic flow. An angle of insonation of 15^{o} was used in the calculation of the study results based on previous measurements when ultrasound imaging was available. Velocity was calculated between the onset of systolic flow for one beat and the onset of systolic flow for the succeeding beat and thus defined a mean flow velocity throughout the cardiac cycle. Since cross-sectional area for the vessel was not obtained in these subjects (although we did make such measurements last year), volumetric flow was not available. Thus, inter-individual comparisons are restricted to those which take account of changes within an individual.

Preliminary observations from data analyzed thus far suggest that Tibetans better maintain arterial oxygen saturation during sleep. Only modest sleep-disordered breathing occurred in the young healthy Tibetan or Han subjects but the few occurrences of sleep-disordered breathing (apneas or hypopnea) appeared more common in Han than Tibetan young men. Measurements of internal carotid artery mean flow velocity carried out in some of the healthy young subjects indicated alterations in mean flow velocity with changes in sleep stages. The mean flow velocity during REM appeared to increase, consistent with observations made previously in experimental animals but never before made in humans, and increases in mean flow velocity appeared to coincide with the episodes of sleep disordered breathing. Thus, alterations in brain blood flow may be important compensatory mechanisms for preservation of brain oxygen delivery in normal subjects.

The second set of studies were carried out in 8 persons (7 Hans and 1 Tibetan) with chronic mountain sickness and 8 persons (7 Hans and 1 Tibetan) of a similar age and duration of high altitude residence were carried out during sleep and wakefulness. We observed that subjects with chronic mountain sickness, consistent with the literature (7,8,12), had blunted hypoxic ventilatory drives. During sleep, measurements made this year indicated severe and widespread episodes of sleep disordered breathing in the chronic mountain sickness group. Ventilatory and brain blood flow measurements were carried out as described above in all the chronic mountain sickness patient and control subjects.

Our purpose was to determine whether a failure for increases in internal carotid artery mean flow velocity occurred in the chronic mountain sickness patients which would further act to exagerate their hypoxemia during sleep. Our initial data analysis suggests that internal carotid artery mean flow velocity was low during wakefulness and failed to rise during episodes of sleep-disordered breathing and accompanying hypoxia and hypercapnia in the chronic mountain

sickness patients. However, this data analysis is currently underway and results are only preliminary at this time.

This year, as well as last year, studies of ventilation and uterine flow were performed in Tibetan and Han pregnant women. These studies were not supported by Army funds but rather by NIH awards to Lorna Moore. Because the results bear on our central hypothesis concerning superior adaptation to high altitude in Tibetans, we will briefly refer to them here. We had made ventilatory measurements and carried out assessment of uterine blood flow last year in approximately 20 Han and 20 Tibetan subjects. However, the subject number upon analysis proved insufficient since several subjects had data of unacceptable quality and not all subjects gave birth in the participating hospitals in Lhasa and hence birth weights were not available. Thus, we studied an additional 8 Tibetan women and 7 Han women this year to increase the sample size. We observed, like last year, that the Tibetan and Chinese women had similar ventilatory characteristics but that lower hemoglobin concentrations in the Tibetan than the Han translated into a reduction in the estimated arterial oxygen content. Birth weights are not yet in hand from the subjects studied this year. If, like last year, the Tibetan babies weigh more than the Han babies, the observation of lower arterial oxygen content is not in keeping with our general hypothesis that increased heavier birth weight babies are born to mothers with greater uterine oxygen delivery (10). However, in addition to arterial oxygen content, uterine blood flow is a major determinant of uterine oxygen delivery. Our measurements this year of uterine artery mean flow velocity and mean flow velocity for the other major vessels supplying the uterine arteries suggested that higher uterine artery mean flow velocity occurred in the Tibetan compared to the Han women. If this increase in mean flow velocity is paralleled by an increase in uterine arterial flow, it suggests that the Tibetan women may have greater uterine oxygen delivery than the Han women.

CONCLUSIONS

We have carried out two successful field seasons in the Fall of 1987 and the Fall of 1988. These studies constitute the first effort to examine the full range of oxygen transport characteristics in Tibetan and Han persons living on the Tibetan Plateau. They suggest that the Tibetan persons may benefit from a series of adaptations resulting in enhanced tissue oxygen supply and/or utilization. Further, they indicate that previous observations based on life-long residents of high altitude and in North and South American may not apply to Himalayan (Tibetan) persons. The Tibetans, unlike other life-long high altitude residents, maintain brisk ventilation and ventilatory responsiveness to hypoxia and hence may be better able to maintain arterial oxygen saturation. In addition the distribution of blood flow may favor high oxygen requiring tissues such as the brain and the uterus and may also be favorable for maintaining oxygen delivery during sleep. Observations also suggest that Han persons who fail to adjust to high altitude suffer from a loss of ventilatory drive, a likely widening of the alveolar-arterial oxygen gradient due to the presence of chronic obstructive lung disease, and a reduced internal carotid artery mean flow velocity (brain blood flow) particularly during sleep.

The implications of the completed research indicate that population differences exist in response to high altitude. Further, they indicate a range of variation within members of a single population that may influence their susceptibility to altitude disorders. For example, not all the Han persons who have lived at altitude for an extended period develop chronic mountain sickness and those individuals who are resistant to this disease appear to benefit from the preservation of ventilatory and brain blood flow responsiveness to hypoxia. Work to be carried out during the third project year will extend our observations and permit us to make direct measurements of cardiac output, arterial-venous oxygen differences, pulmonary arterial pressure, and tissue oxygen utilization. This will allow us to address the flow-related and tissue oxygen extraction components of oxygen transport which, until this time, have only been assessed indirectly.

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APPENDIX

The following are the abstracts and/or manuscripts which have been published or submitted for publication as a result from the investigation carried out under this contract to date.

ABSTRACTS

1. Sun S, Zhang JG, Tao JX, Zhoma ZX, Huang SY, McCullough RG, Reeves CS, Reeves JT, Moore LG. Higher exercise capacities in Tibetan than Han male residents of Lhasa (3658 m). FASEB Journal 2:A1281, 1988.

2. Sun S, Zhang JG, Tao JX, Zhoma ZX, Huang SY, McCullough RG, McCullough RE, Reeves CS, Reeves JT, Moore LG. Higher ventilatory drives in Tibetan than male residents of Lhasa (3658 m). Am Rev Resp Dis 137(4):410, 1988.

3. Sun SF, Huang SY, Zhoma ZX, Zhang JG, Tao JX, McCullough RG, McCullough RE, Reeves JT, Moore LG. Decreased ventilation and hypoxic ventilatory responsiveness are not reversed by naloxone in Lhasa residents with chronic mountain sickness. FASEB Journal (In press), 1989.

4. Story SA, Moore LG. Doppler Ultrasound: A tool for assessment of hemodynamics in high altitude pregnancy. Am J Phy Anthro (In press), 1989.

5. Zhoma ZX, Sun SF, Zhang JG, Huang SY, Moore LG. Fetal growth and maternal 0_2 supply in Tibetan and Han residents of Lhasa (3658 m). FASEB Journal (In press), 1989.

6. Moore LG. Maternal 0_2 transport and fetal growth in Colorado, Peruvian, and Tibetan populations. Am J Phy Anthro (In press), 1989.

MANUSCRIPTS submitted or under preparation

1. Sun SF, Zhoma ZX, Zhang JG, Tao JX, Huang SY, McCullough RG, McCullough RE, Reeves CS, Reeves JT, Moore LG. Greater maximal 0_2 uptake and vital capacities in Tibetan and Han male residents at Lhasa (3658 m). Submitted to Journal of Applied Physiology.

2. Sun SF, Zhoma ZX, Zhang JG, Tao JX, Huang SY, McCullough RG, McCullough RE, Reeves JT, Moore LG. Decreased ventilation in hypoxic ventilatory responsiveness are not reversed by naloxone in Lhasa (3658 m) residents with chronic mountain sickness. MS in preparation for submission to American Review Respiratory Diseases.

3. Sun SF, Zhoma ZX, Zhang JG, Tao JX, Huang SY, McCullough RG, McCullough RE, Reeves JT, Moore LG. Increased ventilatory responsiveness to 0_2 and CO_2 in Tibetan compared to Han male residents of Lhasa, 3658 m.

4. Sun SF, Moore LG. Physiologic adaptation in Himalayan natives (Tibetans) and acclimatized newcomers (Hans). Manuscript in preparation for inclusion in Hypoxia "89". A volume to be edited by J. Sutton, G. Coats, and J Remmers.